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Review

The telomere/telomerase system in autoimmune and systemic immune-mediated diseases

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ABSTRACT

Telomeres are specialized nucleoproteic structures that cap and protect the ends of chromosomes. They can be elongated by the telomerase enzyme, but in telomerase negative cells, telomeres shorten after each cellular division because of the end replicating problem. This phenomenon leads ultimately to cellular senescence, conferring to the telomeres a role of biological clock. Oxidative stress, inflammation and increased cell renewal are supplementary environmental factors that accelerate age-related telomere shortening. Similar to other types of DNA damage, very short/dysfunctional telomeres activate a DNA response pathway leading to different outcomes: DNA repair, cell senescence or apoptosis. During the last 10 years, studies on the telomere/telomerase system in autoimmune and/or systemic immune-mediated diseases have revealed its involvement in relevant physiopathological processes. Here, we present a literature review of telomere and telomerase homeostasis in systemic inflammatory diseases including systemic lupus erythematosus, rheumatoid arthritis and granulomatous diseases. The available data indicate that both telomerase activity and telomere length are modified in various systemic immune-mediated diseases and appear to be connected with premature immunosenescence. Studies on the telomere/telomerase system open new research avenues for the basic understanding and for therapeutic approaches of these pathologies.

Contents

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1. The telomeres and telomerase system

Human chromosomes are capped by telomeres, which consist of tandem repeats of the DNA sequence TTAGGG and their associated proteins. Telomeres protect chromosomes from DNA degradation and end-fusions which could lead to chromosomal breaks and recombination [1]. Telomerase is a reverse transcriptase enzyme, which adds telomeric repeats to the ends of chromosomes, thus compensating the telomeric loss [2] that occurs after each cellular division due to the inability of conventional DNA polymerases to fully replicate the ends of a linear DNA molecule [1,2]. In telomerase negative cells, telomeres shorten after each cellular division until they reach a critical size leading to Mortality 1 check-point (M1) activation resulting in cell senescence. Telomere length thus determines the replication capacity of a cell. According to this telomeric "clock model", telomeres are essential regulators of cell (and, likely, organismal) lifespan [3]. The M1 point is under the control of p53 and/or Rb genes. In case of p53 and/or pRb inactivation, cells continue to divide with persistent telomere erosion and destabilization resulting in DNA breaks, recombination and/or chromosomal ends fusion. Such telomere instability correspond to Mortality 2 check-point (M2) and leads in most of the cases, to apoptosis. However, rare cultured cells can circumvent M2 and become immortalized by reactivating either telomerase enzyme or a recombination-based mechanism to maintain telomere length called ALT (Alternate Lengthening of Telomeres) [3,4].

2. Telomere length and telomerase activity in autoimmune diseases

Many autoimmune and inflammatory diseases are characterized by spontaneous hyperactivity of the immune system including autoantibody production. Although their pathophysiological mechanisms are not completely elucidated, in most of these diseases, inflammation and oxidative stress are parts of the process. Interestingly, inflammation, oxidative stress as well as increased leucocyte renewal are major environmental factors associated with telomeres shortening acceleration [5], suggesting a connection between the telomere/telomerase system and autoimmune and/or inflammatory diseases. In the last decade, this observation, together with data emerging from intensive researches in oncology on the telomere/telomerase system and its potential therapeutic implications, spurred studies assessing the role of this system in the physiopathology of autoimmune and/or inflammatory diseases. We propose a summary of all published articles on this topic (Table 1):

2.1. Systemic lupus erythematosus and other connective tissue diseases

In systemic lupus erythematosus (SLE), a total of 273 patients were studied [6–14]. Telomere length and telomerase activity were measured, in peripheral mononuclear blood cells (PBMC), but also in monocytes, granulocytes [14] and lymphocyte subpopulations (B and T lymphocytes as well as $CD4^+$ and $CD8^+$ T cells and their respective naive and memory subpopulations). Telomere length of PBMC was decreased in SLE, especially in young patients. The telomerase activity was higher in patients than in controls and appeared to correlate to the Disease Activity Index (SLE Disease Activity Index: SLEDAI), especially in B lymphocytes. Immunosuppressive agents seem to induce a telomerase activity decrease, but these results were obtained on a limited group of patients [12]. One group reported 11 patients followed for mixed connective tissue disease who also presented increased telomerase activity [9]. In Sjögren's syndrome telomerase activity in PBMC from 25 patients has been measured and was reported to be increased [9,13].

2.2. Rheumatoid arthritis

In rheumatoid arthritis (RA), PBMC from more than 255 subjects were studied [13,15–18]. Naive and memory $CD4^+$ T cells subpopulations were also analyzed. Telomeres length of PBMC, $CD4^+$ and $CD8^+$ lymphocytes were decreased and this phenomenon was independent of the duration and the severity of the disease [17]. Telomerase activity was higher in RA patients than in controls. Telomeric erosion was strongly related to the HLADRB1 04, since healthy relatives of RA patients as well as healthy controls carrying this HLA allele had shorter telomeres than controls which did not carry this allele [16].

Telomere length of circulating hematopoietic precursor cells ($CD34^+$) was measured among 25 RA patients [19]. Their telomeres were shortened in comparison with controls, especially among patients younger than 30 years. There was no correlation between telomere shortening and disease duration, disease activity or immunosuppressive therapy. Marked telomere erosion found in these cells could indicate proliferative stress-induced senescence. Premature telomere erosion independently of disease activity markers raised the question of whether defective telomere maintenance was an intrinsic defect in RA, rather than the consequence of inflammation and/or immunosuppressive therapy. Fujii et al. studied the telomerase activity of isolated naive $CD4^+$ T cells of RA patients [20]. Upon stimulation, this lymphocyte subset was defective in up-regulating telomerase activity due to hTERT insufficient induction. Overexpression of ectopic hTERT restored proliferative expansion of these cells. Telomerase insufficiency did not affect memory T cells or $CD34^+$ hematopoietic stem cells and was independent from disease activity. These recent results showed that telomerase could have an implication in RA physiopathology.

2.3. Granulomatous diseases: Wegener's granulomatosis and sarcoïdosis

The telomeres length of PBMC was studied among 22 patients with Wegener's granulomatosis. Telomeric erosion was increased among patients with long-term disease ($p<0.001$) and no telomerase activity detected [21]. The telomere length in $CD28^-$ T cells was significantly decreased in patients when compared to non-immune renal nephritis patients. The results obtained on this quite small cohort of patients and showing that $CD28^-$ T cells were highly senescent, led authors to suggest that a portion of T cells could have undergone replicative senescence, which in turn indicates clonal expansion of T cells as a consequence of activation [21,22]. The telomeres length of PBMC was studied among 111 patients with sarcoïdosis. Telomeric erosion was found more frequently than in controls ($p<0.001$) [23].

2.4. Systemic sclerosis

In systemic sclerosis, PBMC from a total of 114 subjects have been studied [9,13,24,25]. Three authors reported telomeric erosions in 71 patients (presenting diffuse or limited systemic sclerosis), but also

Table 1
Telomeres and telomerase in autoimmune and/or systemic diseases.

Author	Disease	Studied cells	Telomere length measure-ment	Telomerase activity analysis	Number of patients	Results
Honda [8]	SLE	PBMC	Yes	Yes	$n=58$	Telomeric erosion except on memory $CD8^+CD28-$T cells
Katayama [9]	SLE	PBMC	ND	Yes	$n=17$	Elevated TA
Kurosaka [11]	SLE	PBMC	Yes ($n=30$)	Yes ($n=55$)	$n=30$ $n=55$	Telomeric erosion TA correlated to SLEDAI
Klapper [10]	SLE	PBMC	Yes ($n=5$)	Yes ($n=9$)	$n=5$ $n=9$	Elevated TA in $CD19^+$ B cells TL identical
Kurosaka [12]	SLE	PBMC, T and B lymphocytes	Yes	Yes	$n=34$	Elevated TA, especially in B cells and if elevated SLEDAI
Fritsch [7]	SLE	Lymphocyte sub populations	Yes	Yes	$n=7$	Telomeric erosion when naïves $CD4^+$ T cells differentiate
Tarhan [13]	SLE	PBMC	ND	Yes	$n=15$	Elevated TA
Beier [6]	SLE	PBMC: T cells (CD4/CD8); B cells and monocytes	Yes (flow fish)	ND	$n=22$	No correlation between TL and disease activity
Wu [14]	SLE	PBMC=> monocytes (MNC) Neutrophilic granulocytes (NG)	Yes	Yes	$n=60$	In MNC and NG, telomeric erosion correlated to SLEDAI. No TA in NG
Katayama [9]	Mixed connective tissue disease	PBMC	ND	Yes	$n=11$	Elevated TA
Yudoh [18]	RA	Blood and synovial peripheral lymphocytes	ND	Yes	$n=18$	Elevated TA
Koetz [15]	RA	PBMC lymphocytes $CD4^+$ ($45RA^-/45RO^+$); $CD8^+$	Yes	ND	$n=51$	Telomeric erosion
Schönland [16]	RA	PBMC lymphocytes $CD4^+$ ($45RA^-/45RO^+$)	Yes	Yes	$n=37$	Premature telomeric erosion in presence of DRB1 04HLA
Steer [17]	RA	PBMC	Yes	ND	$n=176$	Telomeric erosion independent from length and severity of RA
Tarhan [13]	RA	PBMC	ND	Yes	$n=10$	Elevated TA
Colmegna [19]	RA	$CD34^+$ hematopoietic precursor cells	Yes	ND	$n=25$	Telomeric erosion
Fujii [20]	RA	Naive $CD4^+$ T cells	ND	Yes	$n=38$	Impaired induction of TA in naïve $CD4^+$ T cells
Guan [23]	Sarcoidosis	PBMC	Yes	ND	$n=111$	Telomeric erosion
Vogt [21]	Wegener's granulomatosis	PBMC	Yes	Yes	$n=22$	No TA Telomeric erosion
Tarhan [13]	Systemic sclerosis	PBMC	ND	Yes	$n=19$	Decreased TA
Artlett [24]	Systemic sclerosis	Lymphocytes	Yes	ND	$n=43$ and 183 relatives	Telomeric erosion among patients and healthy parents
Katayama [9]	Systemic sclerosis	PBMC	ND	Yes	$n=9$	TA identical to controls
MacIntyre [25]	Limited systemic sclerosis	PBMC	Yes	ND	$n=43$	In limited sclerosis: telomere are longer than controls
Tarhan [13]	Sjögren's syndrome	PBMC	ND	Yes	$n=14$	Elevated TA
Katayama [9]	Sjögren's syndrome	PBMC	ND	Yes	$n=11$	Elevated TA
Kurosaka [27]	Adult-onset Still's disease	PBMC	ND	Yes	$n=2$	Elevated TA correlated to disease activity
Prelog [26]	Juvenile idiopathic arthritis	$CD4^+CD45RA^+$T cells	Yes	No	$n=22$	Increased telomeric erosion in $CD4^+CD45RA^+$ naïve T cells
Morosetti [28]	Inclusion-body myositis	Primary muscle cells	Yes	ND	$n=8$	Telomeric erosion
Wu [29]	Atopic dermatitis (D) and psoriasis (P)	PBMC, lymphocytes $CD4^+$ ($45RA^-/45RO^+$); $CD8^+$ ($28^-/28^+$)	Yes	Yes	D: $n=32$ P: $n=16$	Elevated TA ($CD4^+$ T cells) Telomeric erosion (memory T cells)
Sasaki [30]	Primitive biliary cirrhosis	Biliar epithelial cells	Yes	ND	$n=13$	Telomeric erosion compared to normal bile ducts cells
Tsakiri [32]	Idiopathic pulmonary fibrosis	PBMC	Yes	Yes		Telomeric erosion No TA Identification of *TERT* or *TERC* mutations
Armanios [31]	Idiopathic pulmonary fibrosis	PBMC	Yes	Yes		Telomeric erosion No TA Identification of *TERT* or *TERC* mutations
Jeanclos [33]	Type I diabetes	PBMC	Yes	ND	$n=54$	Telomeric erosion
Fyhrquist [35]	Type I diabetes	Whole blood	Yes	ND	$n=132$	Telomeric erosion among progressor patients

Abbreviations: ND: Not done; PBMC: Peripheral Blood Mononuclear Cells; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; TA: Telomerase activity; TERT: Telomerase reverse transcriptase; TERC: Human telomerase RNAcomponent; and TL: Telomere length.

among their healthy relatives [9,13,24]. Telomerase activity was decreased or identical to non-relatives controls. These results raise the possible role of an association of the telomere/telomerase system alteration together with environmental factors and/or a genetic predisposition leading to disease development in these patients. Another group recently reported 43 patients with limited systemic sclerosis: telomere length did not differ significantly from that of healthy controls before 50 years of age, whereas it was even longer in

systemic sclerosis patients than controls after 50 years [25]. However, only patients with limited systemic sclerosis were enrolled in this study.

2.5. Juvenile idiopathic arthritis and adult-onset Still disease

One research team recently reported 22 patients with juvenile idiopathic arthritis [26], by studying telomere length of peripheral naive $CD4^+CD45RA^+$ T cells. Patients showed shorter telomere length than controls suggesting that the patient's T cells underwent age-inappropriate senescence. Kurosaka et al. found increased telomerase activity correlated to the disease activity in PBMC of two patients with adult-onset Still disease [27].

2.6. Myositis, psoriasis and atopic dermatitis

Morosetti et al. studied telomere in primary muscular cells from 8 patients with inclusion-body myositis [28]. When compared to control cells, the proliferative rate of patients's cells was decreased ($p<0.05$), thus indicating that proliferative capacity of sporadic inclusion-body-myositis muscle cells becomes exhausted earlier. The telomere length of these cells was shorter than controls ($p<0.02$), suggesting premature senescence. Therefore, these patients's myoblasts seem to have a constitutively impaired regenerative capacity.

Lymphocytes from 32 subjects with atopic dermatitis and 16 patients with psoriasis were studied [29]. Telomere erosion and increased telomerase activity were found in $CD4^+$ T cells, predominantly in memory T cells, in comparison with controls.

2.7. Primary biliary cirrhosis

Telomere length were significantly shortened in biliary epithelial cells of the most damaged bile ducts of patients with primary biliary cirrhosis when compared to normal liver ($n=13$, $p<0.01$) [30]. Telomere dysfunction, detected through DNA damage was also studied: γH2AX-DNA damage foci in these patients's small bile ducts and bile ductules were present in 55.6% ($n=133$) versus almost none of the control normal livers ($p<0.01$). These results, showing telomere shortening and an accumulation of DNA damage in damaged bile ducts, characterize biliary cellular senescence and may play a role in the following progressive bile duct loss in primary biliary cirrhosis.

2.8. Idiopathic pulmonary fibrosis

Recently, two research teams identified mutations in telomerase complex genes (*hTERT* and *hTR*) [31,32] in idiopathic pulmonary fibrosis. Armanios et al. reported heterozygous mutations of *hTERT* ($n=5$) and *hTR* ($n=1$) among 6 patients with familial idiopathic pulmonary fibrosis [31]. These patients presented PBMC's shortened telomere compared to age-matched controls ($p<0.006$) and altered telomerase activity. Tsakiri et al. analyzed 46 families with idiopathic interstitial lung disease and also identified heterozygous mutations in *hTERT* or *hTR* in 12% of their cohort [32]. When compared to age-matched controls, their mutated patients also displayed shortened telomere length.

2.9. Autoimmune diabetes

In type I diabetes, PBMC from 54 patients were compared to controls and type II diabetic patients: telomere erosion was found specifically in type I diabetes and not in type II diabetes [33]. Indeed, the phenomenon could not be related to hyperglycemia but to autoimmunity by a still unknown mechanism. Very recently, Fyhrquist et al. analyzed the telomere length of whole blood of 132 patients compared to 44 healthy controls. They found out that short telomeres were an independent predictor factor of diabetic nephropathy progression.

In summary, the telomere length of peripheral blood mononuclear cells (PBMC) is shorter, when compared to age-matched healthy controls, in patients with systemic lupus erythematosus [7,8,11,12,14], rheumatoid arthritis [15–17,34], Wegener's granulomatosis [21], sarcoidosis [23], systemic sclerosis [24], idiopathic pulmonary fibrosis [31,32] and type I diabetes [33,35]. The same phenomenon is observed among specific cell subsets as follows: naive $TCD4^+C45RA^+$ cells in juvenile idiopathic arthritis [26]; $TCD4^+$, $TCD8^+$ and $CD34^+$cells in rheumatoid arthritis [15,16,19]; $TCD28^+$ cells in Wegener's granulomatosis [21] as well as $TCD4^+$ cells in psoriasis or atopic dermatitis [29]. Furthermore, the telomere length of specific target-tissue cells was also shorter in inclusion-body myositis (primary muscular cells) [28] and in primary biliary cirrhosis (biliary epithelial cells of the most damaged bile ducts) [30].

Thus, it seems clear from these studies that a general pattern of increased telomere shortening characterizes cells of patients suffering from systemic disease.

3. Possible reasons of telomeric erosion

In all the aforementioned pathologies, there is often an associated inflammatory syndrome, which can lead to cellular oxidative stress. On the other hand, an increased leucocyte renewal in patients with systemic immune-mediated diseases could also contribute to the acceleration of telomere shortening.

Concurrently, there may be a suboptimal telomerase activity in most of these pathologies. Indeed, an elevated level of telomerase activity was found in PBMC of patients with systemic lupus erythematosus [7–13,36], connective tissue disease [9,13], rheumatoid arthritis [13,16,18] (while decreased telomerase activity was measured in their naive $TCD4^+$ cells [20]) and Sjögren's syndrome [9,13] as well as in $TCD4^+$ cells of patients with psoriasis and atopic dermatitis [29]. By contrast, telomerase activity was not detected in PBMC from Wegener's patients [21] and was decreased among patients with systemic sclerosis [24] or idiopathic pulmonary fibrosis [31,32] when compared to healthy age-matched controls.

Lastly, accelerated telomere erosion could be due to chronic stress exposure. The recently Nobelized Elisabeth Blackburn has worked with psychiatrists and has found out that chronic stress is correlated to short leukocyte telomere length, a phenomenon attributed to higher levels of oxidative stress at the cellular level [37]. Indeed, the group of patients with the highest psychological stress presented shorter telomeres and lower telomerase activity in their PBMC when compared to the low stress-group of patients. These elements suggest that psychological functions could have a direct impact on the telomere/telomerase system. Autoimmune diseases are often chronic and affect young patients, which means that patients have to live with their disease for many years or even all their life. Such a condition can influence their psychological balance and be responsible for stressful conditions, which could in turn be responsible for increased telomeric erosion in PBMC, as seen in these pathologies.

4. Consequences of telomeric erosion

In the past years, it has become clear that telomeres are directly responsible for sustained DNA damage signals in senescent cells, and DNA damage foci localized on telomeres in senescent cells can readily be detected *in vivo* [38–40]. DNA damage signals can originate from short telomeres and contribute to p53 or pRb activation leading to DNA damage repair [39,40], apoptosis or permanent cell-cycle arrest corresponding to a senescent state of the cell. This phenomenon, which contributes to safeguard the genome and cell integrity, may, when exaggerated, lead to premature senescence and tissue

degeneration. By contrast, inhibition of apoptosis or senescence can lead to cell modifications resulting in loss of tolerance of the immune system.

The connection between the telomere/telomerase system dysfunction and the previously described systemic immune-mediated diseases has not yet been clearly established. However, it has been hypothesized that telomeric erosion could lead to accelerated senescence of the immune system [41], in particular in lymphocytes subpopulations. Thus, if premature immunosenescence affects differently naive and effector T cells and that autoreactive T cells survive longer than other T cells including regulatory clones, cytotoxic autoaggressive lesions could occur [20]. In addition, escape of senescent effector T cells from the regulatory confines of the normal immune system may induce cytotoxic activities responsible for tissues destructions. Finally, replicative senescence of regulatory T cells could cause deficiency of anti-inflammatory and anti-autoimmune processes. However, studies are currently missing specifically addressing the question of telomere length/telomerase activity in regulatory T cells. Therefore, it would be interesting to assess telomere length and telomerase activity in regulatory T cells of patients with such diseases.

In addition, apoptosis clearance deficiencies that could induce the loss of tolerance in lymphoid tissues were pointed out in systemic lupus erythematosus and rheumatoid arthritis [42–44].

It is also interesting to note that premature tissue degeneration is observed in autoimmune diseases, such as primary biliary cirrhosis (biliary ducts damages) [30], inclusion-body myositis (primary muscular cells) [28] and/or rheumatic arthritis (joint) [18]. Interestingly, these pathologies are characterized by an inflammatory process initiated by the immune cells on target tissues during which free radicals get liberated, perhaps damaging telomeres and increasing their erosion rate [5]. Interestingly, telomere dysfunction, detected through DNA damage was studied in primary biliary cirrhosis: γH2AX-DNA damage foci in these patients' small bile ducts and bile ductules were present in 55.6% ($n=133$) versus almost none of the control normal livers ($p<0.01$). These results, showing telomere shortening and an accumulation of γH2AX-DNA damage foci in the most damaged bile ducts as well as expression of $p21^{WAF1/Cip}$ and $p16^{INK4a}$, could indicate premature biliary cellular senescence, which may play a role in the progressive bile duct loss in primary biliary cirrhosis. Such a phenomenon, in absence of a sufficient telomerase activity, could alter the tissue regeneration process leading to premature organ degradation and dysfunction when compared to healthy age-matched individuals. It would then be interesting to measure telomere length in the different target tissues during such diseases.

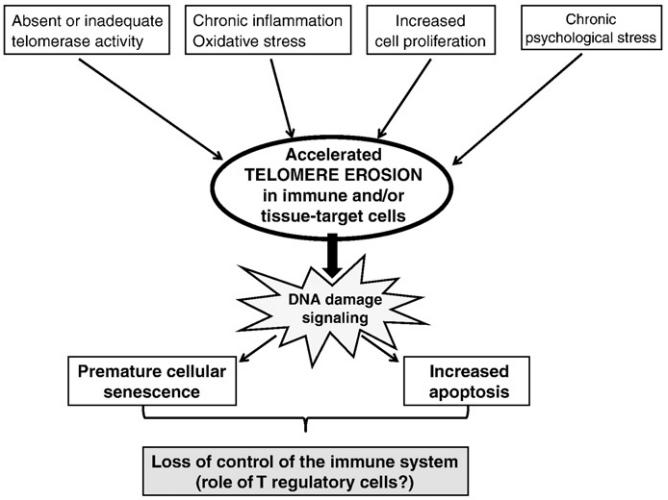

Fig. 1. A Proposed model for the telomere/telomerase system's potential involvement in the pathophysiology of "systemic diseases". Several elements, including absent or inadequate telomerase activity, chronic inflammation (and thus oxidative stress), increased cell proliferation and chronic psychological stress, could affect cellular telomere length in immune and/or tissue-target cells. In these cells, telomere erosion could lead to premature cellular senescence and increased apoptosis, possibly by the DNA damage signaling pathway. All together, these cellular phenomenons could be responsible of a loss of control of the immune system in which the role of regulatory T cells remains to be evaluated.

5. Conclusion

The analysis of the literature relating the telomere/telomerase system to systemic immune-mediated diseases suggests that this system could be involved through different mechanisms, which are summarized in Fig. 1. An accelerated telomeric erosion in PBMC could result from chronic stress exposure, increased oxidative stress and/or suboptimal telomerase activity in a context of high PBMC renewal. This could result in a premature senescence of immune cells and specific target-tissue cells. These observations could be extended to prospective studies among large populations with easy, reproducible and comparable techniques measuring telomere length and telomerase activity, in order to better elucidate the involvement of the telomere/telomerase system in the pathophysiology of systemic immune-mediated diseases. In the future, these works could lead to new therapeutic strategies for these diseases, which often have neither specific nor curative treatments.

Take-home messages

- The telomere/telomerase system plays many roles, including protection of the genome integrity and regulating cellular aging and cell lifespan.
- In peripheral blood mononuclear cells of patients with autoimmune and systemic immune-mediated diseases, telomeres are shortened.
- In these diseases, telomeric erosion could result from
  a. chronic psychological stress exposure
  b. inflammation and thus increased oxidative stress
  c. absent or inadequate telomerase activity
- Alteration of the telomere/telomerase system in autoimmune diseases could reflect premature senescence of immune cells and specific tissue-target cells.

Conflict of interest

There was none declared.

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Serum levels of BAFF for assessing the disease activity of Takayasu arteritis

Takayasu arteritis (TA) is a chronic vasculitis that affects large elastic arteries. Monitoring of disease activity is crucial because the disease may progress despite treatment with glucocorticoids. Elevated levels of B cell activating factor (BAFF) have been observed in patients with autoimmune diseases. In this study, **Nishino Y. et al. (Clin Exp Rheumatol 2010; 28: S14–S17)**, investigated whether dysregulation of BAFF occurs in TA. Serum levels of BAFF were measured in sera of 9 patients with TA including 6 patients with follow-up after induction therapy. Circulating BAFF levels in TA patients were higher than in those in healthy subjects. The high levels of BAFF in active TA patients were decreased when the patients entered remission. This is the first study to show elevated levels of BAFF in active TA patients. These findings suggest that this cytokine contributes to vasculitis in TA and raise the possibility that monitoring of serum BAFF might aid clinicians in making adequate treatment adjustments in TA patients.

Prevalence of anti-endothelial cell antibodies in patients with pulmonary arterial hypertension associated with connective tissue diseases

The prevalence of anti-endothelial cell antibodies (AECAs) in the sera of connective tissue diseases (CTD) patients with pulmonary arterial hypertension (PAH) and its correlation with clinical manifestations was investigated. **Lin MT. et al. (Chin Med Sci J 2010; 25: 27–31)**. AECAs in sera of 39 CTD patients with PAH, 22 CTD patients without PAH, and 10 healthy donors as controls were detected with Western blotting. The prevalence of different AECAs in different groups was compared and its correlation with clinical manifestations was also investigated. The prevalence of AECAs was 82.1%in CTD patients with PAH, 72.7% in CTD patients without PAH, and 20.0% in healthy donors. Anti-22kD AECA was only detected in CTD patients with PAH (15.4%). Anti-75kD AECA was more frequently detected in CTD patients with PAH than those without PAH (51.3% vs 22.7%, $p<0.05$). In CTD patients with PAH, anti-75 kD AECA was more frequently detected in those with Raynaud's phenomenon or with positive anti-RNP antibody. Thus, AECAs could be frequently detected in CTD patients with or without PAH, while anti-22kD and anti-75kD AECA might be specific in CTD patients with PAH.